PATENT SPECIFICATION

NO DRAWINGS

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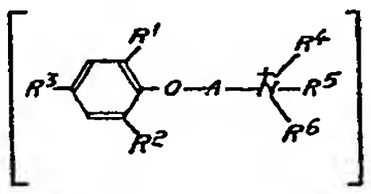
COMPLETE SPECIFICATION

Quaternary Ammonium Compounds and their preparation

We, THE WELLCOME FOUNDATION LIMITED, a British Company of 183—193 Euston Road, London, N.W.1, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed to be particularly described in and by the following statement:—

The present invention relates to quaternary ammonium compounds and the preparation thereof.

In British Patent Specification No. 765,850 there are described quaternary ammonium salts containing the cation (I):—



(I)

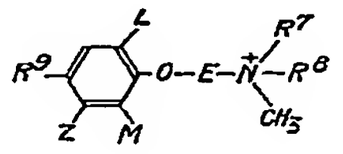
in which R^1, R^2, R^3 each represent a hydrogen or halogen atom or a lower alkyl group with not more than one of R^1, R^2, and R^3 representing a hydrogen atom, A represents

$-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH(CH_3)-CH_2-$, or $-CH_2-CH(CH_3)-$

and R^4, R^5 and R^6 each represent a lower alkyl group, that is an alkyl group containing not more than 4 carbon atoms. Such compounds are described as being potent local anaesthetics.

It has also been shown that certain compounds falling within the above general formula, in particular 2 - (2,6 - dimethylphenoxy)ethyltrimethylammonium bromide (TM 10), have a sympatholytic action (Bain and Fielden, Lancet 1958 (2), page 472; Exley, *British Journal of Pharmacology and Chemotherapy*, Volume 12, (1957) page 297), but a clinical trial in patients with high blood pressure indicates that TM 10, though effective as an antihypertensive agent, is too toxic for human use because of its parasympathomimetic properties.

We have now found that a series of new quaternary ammonium compounds containing a cation of the formula (II) have a specific sympatholytic action, in that they depress the peripheral sympathetic nervous system and are free or relatively free from the unwanted parasympathomimetic properties. Consequently these compounds are superior to TM 10 and known analogues, and some are also considerably more potent than TM 10.



(II)

In this and succeeding formulae:

R^7 and R^8 are the same or different and are each methyl, ethyl, or 2 - hydroxyethyl groups; and

R^9 is an acetyl, phenacetyl, propionyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, acetamido, or propionamido group in the circumstances when E is a $-CH_2-CH_2-$ group, and L and M are the same or different and are each hydrogen or halogen atoms or methyl, ethyl, or methoxy groups, and Z is a hydrogen atom;

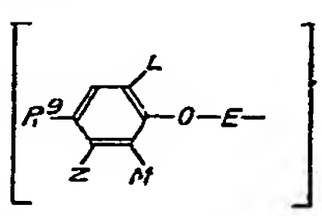
R^9 is a benzoyl group (wherein the phenyl group is optionally substituted in any one position by a halogen atom or an alkyl or alkoxy group containing from one to four carbon

atoms, or a nitro or free amino group) in the circumstances when E is a $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH(CH_3)-CH_2-$ or $-CH_2-CH(CH_3)-$ group, and L and M are the same or different and are each hydrogen or halogen atoms or methyl, ethyl or methoxy groups, and Z is a hydrogen atom or hydroxy group.

According to the present invention in one aspect, therefore, there are provided quaternary ammonium compounds containing the cation defined in formula (II).

The preferred cations of the present invention are the *N* - (2 - 4^1 - benzoyl - 2^1,6^1 - dimethylphenoxyethyl) - *N*,*N*,*N* - trimethyl - ammonium, *N* - (2,4^1 - benzoyl - 2^1 - bromophenoxyethyl) - *N*,*N*,*N* - trimethylammonium, *N* - (2-4^1 - benzoyl - 2^1 - bromophenoxy - ethyl) - *N* - ethyl - *N*,*N* - dimethylammonium, *N* - (2-4^1 - benzoyl - 2^1 - bromo - 6^1 - methylphenoxyethyl) - *N*,*N*,*N* - trimethylammonium, *N* - (2-4^1 - *p* - methoxybenzoyl - 2^1,6^1 - dimethylphenoxyethyl) - *N*,*N*,*N* - trimethyl - ammonium, *N* - (2-4^1 - ethoxycarbonyl - 2^1, 6^1 - dimethylphenoxyethyl) - *N*,*N*,*N* - tri - methylammonium, and *N* - (2-4^1 - acetamido-2^1,6^1 - dimethylphenoxyethyl) - *N*,*N*,*N* - trimethylammonium cations.

The compounds of the present invention may be prepared in the manner usual and well known for the preparation of quaternary ammonium compounds, namely by a quaternisation reaction which may be defined as the reaction of a tertiary amine containing three of the four groups desired in the quaternary ammonium compound (namely the phenoxyalkyl group as defined in formula (III), hereinafter referred to as R^{10} and the R^7, R^8, and CH_3 groups) with a reactive derivative of the group it is desired to introduce.



(III)

For example, a tertiary amine of formula $R^7R^8CH_3N$, $R^8R^{10}CH_3N$, $R^7R^{10}CH_3N$, or $R^7R^8R^{10}N$, may be quaternised respectively by a molecular proportion of a reactive ester of the hydroxy derivative of the R^{10}-, R^7-, R^8-, or methyl group, such as a halide or *p*-toluenesulphonate. In practice it is generally preferable to use rather more than the theoretically required proportion of the $R^7R^8CH_3N$ or the reactive derivative of the R^7-, R^8-, or methyl group.

The tertiary amine may be formed *in situ*. For example, if R^7 and R^8 are to be the same or if R^7 or R^8 is to be a methyl group, a phenoxyalkyl secondary amine may be reacted with two molecular proportions of a reactive ester of methanol or ethanol or a reactive monoester of ethylene glycol, such as a methyl, ethyl, or 2-hydroxyethyl halide of *p*-toluenesulphonate or dimethyl or diethyl sulphate, in the presence of an acid binding agent. One molecular proportion will form the tertiary amine while the other will quaternise this tertiary amine to the desired compound. Similarly, if R^7 and R^8 are both to be methyl groups, a primary phenoxyalkylamine $R^{10}NH_2$ may be reacted with three molecular proportions of a reactive ester of methanol, for example a methyl halide or *p*-toluenesulphonate or dimethyl sulphate, in the presence of an acid binding agent. In these reactions, better yields of the desired compound are obtained in practice by using rather more than the theoretically required proportions of the reactive aliphatic derivative.

When R^9 is to be a benzoyl group carrying a free amino group, it is necessary to modify the above described process of preparation of the compounds of the present invention, by providing that in the reactants taking part in the quaternisation reaction there is present in R^9, instead of the free amino group itself, a group capable of conversion to a free amino group, for example a nitro group, and that subsequently this group is converted into the desired free amino group by reduction.

The quaternary ammonium salt produced by the above described reactions may be converted by double decomposition, either during or after the reaction, for example in solution or on an ion exchange column, into the quaternary ammonium salt of another anion.

According to the present invention in yet another aspect, therefore, there is provided the above described process of preparation of the compounds of the present invention.

The compounds of the present invention may be presented in pharmaceutical preparations prepared by any of the well - known methods of pharmacy.

For oral administration, fine powders or granules of the compounds may contain diluents and dispersing and surface active agents, and may be presented in a draught in water or in a syrup, in capsules, or cachets in the dry state or in a non-aqueous suspension, when a suspending agent may be included; in tablets, when binders and lubricants may be included; or in a suspension in water or a syrup or an oil, or in a water/oil emulsion, when flavouring, preserving, suspending, thickening, and emulsifying agents may be included. The granules or the tablets may be coated.

For parenteral administration, the compounds may be presented in aqueous injection solutions which may contain antioxidants, buffers, bacteriostats, agents which solubilise a relatively insoluble compound, and solutes which render the salts isotonic with the blood;

in aqueous suspensions when suspending agents and thickening agents may be included; or in non-aqueous solutions and suspensions if the compound is affected by water. Extemporaneous injection solutions may be prepared from sterile pills, granules, or tablets which may contain diluents, dispersing and surface active agents, binders and lubricants.

The compounds may also be presented in suppositories or pessaries by incorporation in a suppository base.

According to the present invention in yet another aspect, therefore, there are provided the above described pharmaceutical preparations comprising the compounds of the present invention together with a suitable carrier therefor, and the methods of making such preparations.

The invention will now be described by reference to the following examples, in which all temperatures are given in degrees Centigrade.

EXAMPLE 1

4 - Hydroxy - 3,5 - dimethylbenzophenone (136 g.) was added to a solution of sodium (13.8 g.) in hot ethanol (950 ml.) and was followed by ethylene dibromide (136 g.). The resulting mixture was stirred and heated to reflux for 7 hours. About 700 ml. of ethanol was removed by evaporation *in vacuo;* the residue was poured into water (500 ml.). The precipitated oil was extracted with ether and the resulting ethereal solution was exhaustively washed with aqueous 5*N*-sodium hydroxide to remove unchanged starting material. The residual solution was dried with solid potassium carbonate, filtered and evaporated. The residue was distilled *in vacuo* to give 1 - (4 - benzoyl-2,6 - dimethylphenoxy) - 2 - bromoethane, boiling point 182—186°/0.01 mm., freezing point 76°.

A mixture of this substance (16.7 g.) in methanolic dimethylamine (25% w/w; 50 g.) was heated in a sealed tube at 100° for 6 hours. The resulting mixture was evaporated on a steam-bath and excess aqueous 5*N* - sodium hydroxide added to the residue. The precipitated oil was extracted with ether. The ethereal solution was washed with water, dried over potassium carbonate, filtered and evaporated. The residue was distilled *in vacuo* to give 1 - (4 - benzoyl - 2,6 - dimethylphenoxy) - 2 - dimethylaminoethane, boiling point 162—167°/0.001 mm.

Methyl iodide (4 g.) was added to a solution of this base (4 g.) in acetone. Warming took place with the separation of a crystalline solid. After 1 hour the mixture was heated to reflux for 30 minutes, cooled and filtered. The residual *N* - (2-4^1 - benzoyl - 2^1,6^1 - dimethylphenoxyethyl) - *N*,*N*,*N* - trimethyl - ammonium iodide was recrystallised from ethanol, melting point 208—209°.

EXAMPLE 2

Ethyl iodide (5 g.) was added to a solution of 1 - (4 - benzoyl - 2,6 - dimethylphenoxy)-2 - dimethylaminoethane (prepared as described in Example 1 (4 g.) in acetone (10 ml.). Self-warming took place accompanied by the separation of a crystalline solid. After 1 hour, the mixture was heated to reflux for 30 minutes, cooled and diluted with ether. The resulting *N* - (2-4^1 - benzoyl - 2^1,6^1 - dimethylphenoxyethyl) - *N* - ethyl - *N*,*N* - dimethylammonium iodide was recrystallised from ethanol, melting point 185—186°.

EXAMPLE 3

A suspension of 1 - (4 - benzoyl - 2,6 - dimethylphenoxy) - 2 - bromoethane (prepared as described in Example 1) (25 g.) in alcoholic trimethylamine (33% w/w; 40 g.) was heated in a sealed tube for 8 hours at 100°. The cooled reaction mixture was poured into ether. The precipitated solid was filtered off and recrystallised from isopropanol to give pure *N*-(2-4^1 - benzoyl - 2^1,6^1 - dimethylphenoxy - ethyl) - *N*,*N*,*N* - trimethylammonium bromide, melting point 204—205°.

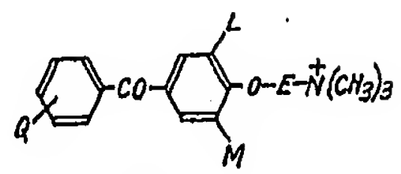
EXAMPLE 4

1 - Bromo - 2 - (2,6 - dimethylphenoxy) ethane (22.9 g.; 0.1 mole.) was slowly added to a suspension of anhydrous aluminium chloride (13.3 g.; 0.1 mol.) in carbon disulphide (75 ml.) with stirring. *p* - Toluoyl chloride (15.5 g.; 0.1 mol.) was then added over a period of 1 hour, the resulting mixture heated at 45—50° for 1 hour and then decomposed with ice and hydrochloric acid in the usual way. The precipitated oil was taken up into ether. The extract was washed with water, dried over potassium carbonate, filtered and evaporated. The residue was distilled *in vacuo* to give 1 - bromo - 2 - (2,6 - dimethyl - 4 - *p*-toluoylphenoxy)ethane, boiling point 185—195°/0.001 mm. It subsequently crystallised and was then recrystallised from isopropanol, melting point 60—61°.

This bromide (8 g.) and ethanolic trimethylamine (33% w/w; 14 g.) were heated together in a sealed tube for 12 hours at 100°. After cooling, the contents of the tube were poured into ether. The resulting *N* - (2 - 2^1,6^1-dimethyl - 4^1 - *p* - toluoylphenoxyethyl) - *N*,*N*,*N* - trimethylammonium bromide was filtered off, washed with ethyl acetate and recrystallised from a mixture of ethanol and isopropanol (1:1) as a semihydrate, melting point 216—217°.

In Table (I) are listed additional 4 - benzoylphenoxyalkyl bromides which were prepared by the method described in Example 4. These were then reacted with trimethylamine, as in Example 4, to give the corresponding *N* - 4 - benzoylphenoxyalkyl - *N*,*N*,*N* - trimethylammonium bromides, of formula (IV) wherein Q is the substituent in the phenyl ring of the benzoyl group.

TABLE I



(IV)

Example No.	Q	L	M	E	Melting (m.p.) or boiling point (b.p.) of the intermediate bromide	Melting point of the quaternary ammonium bromide
5	*m*-CH_3	CH_3	CH_3	—$(CH_2)_2$—	181—186°/0.001 mm. (b.p.) 65—66° (m.p.)	221°
6	*o*-Cl	CH_3	CH_3	—$(CH_2)_2$—	203—206°/0.005 mm. (b.p.) 70—71° (m.p.)	204—205°
7	*m*-Cl	CH_2	CH_3	—$(CH_2)_2$—	97.5—98.5° (m.p.)	203—204°
8	*p*-Cl	CH_3	CH_3	—$(CH_2)_2$—	98—99° (m.p.)	226—227°
9	*o*-CH_3O	CH_3	CH_3	—$(CH_2)_2$—	200—210°/0.001 mm. (b.p.) 195—206°/0.006 mm. (b.p.)	216—217°
10	*m*-CH_3O	CH_3	CH_3	—$(CH_2)_2$—	74—75° (m.p.)	176—178°
11	*p*-CH_3O	CH_3	CH_3	—$(CH_2)_2$—	242—244°/0.001 mm. (b.p.) 52—53° (m.p.)	189—190°
12	*p*-C_2H_5O	CH_3	CH_3	—$(CH_2)_2$—	214—220°/0.01 mm. (b.p.) 79—80°	203°
13	*p*-NO_2	CH_3	CH_3	—$(CH_2)_2$—	108.5—109.5° (m.p.)	240—241°
14	—	Cl	Cl	—$(CH_2)_2$—	146—147° (m.p.)	186°
15	—	—	—	—$(CH_2)_2$—	172—178°/0.002 mm. (b.p.) 186—188°/0.001 mm. (b.p.)	196—197°
16	—	CH_3	CH_3	—$(CH_2)_3$—	77—79° (m.p.)	160—161°

Example 17

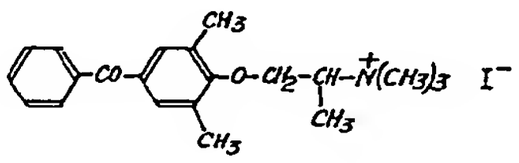
4 - Hydroxy - 3,5 - dimethylbenzophenone (13.6 g.) was added to a solution of sodium (1.4 g.) in methanol (20 ml.) and the resulting clear solution was evaporated *in vacuo*. The residue was dissolved in acetone (50 ml.).

2 - Chloro - 1 - dimethylaminopropane hydrochloride (9.4 g.) was dissolved in cold water (7 ml.); ether (50 ml.) was added and then potassium carbonate (15 g.) with cooling. After thorough shaking, the aqueous layer was removed and re-extracted with fresh ether.

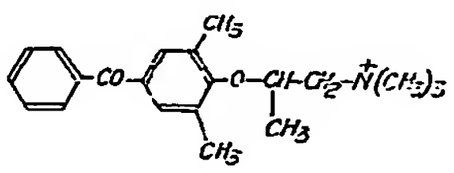
The combined ethereal solutions were added to the above acetone solution and this mixture was evaporated until the temperature of the reaction mixture reached 55—60°, when the bulk of the ether had been removed. The residue was then heated to reflux for 4 hours. The resulting mixture was filtered and the filtrate evaporated. The residue was distributed between ether and 2*N* - hydrochloric acid. (Evaporation of the ethereal solution gave unchanged 4 - hydroxy - 3,5 - dimethylbenzophenone). The acid solution was basified with solid potassium carbonate. The precipitated oil was isolated with ether and distilled *in vacuo*, boiling point 160—163°/0.001 mm. As shown, below, it was a mixture of:

1 - (4 - benzoyl - 2,6 - dimethylphenoxy) - 2 - dimethylaminopropane and 2 - (4 - benzoyl - 2,6 - dimethylphenoxy) - 1 - dimethylaminopropane.

This mixture of bases was dissolved in acetone (20 ml.) and methyl iodide (6 g.) was added. A spontaneous reaction ensued with the separation of a colourless solid. After 30 minutes, the mixture was heated to reflux for 15 minutes. Ether was added to complete the separation. The resulting solid was filtered off and recrystallised from isopropanol containing 5% ethanol as mixed crystals, melting point 166—180°. This material was crystallised four times from ethanol, when it finally had a melting point of 215—216°, this melting point being unchanged on further crystallisation. This material was subsequently shown to be *N* - (2 - 4¹ - benzoyl - 2¹,6¹ - dimethyl - phenoxy - 1 - methylethyl) - *N,N,N* - trimethylammonium iodide (see Example 18).



Evaporation of the alcoholic mother liquors to a small volume afforded a solid, melting point of 166—167°. This product was crystallised once from water and then twice from ethanol to give a product, melting point 166—167°. This material was subsequently identified as *N* - (2-4¹-benzoyl-2¹,6¹ - dimethyl - phenoxy - 2 - methylethyl) - *N,N,N* - trimethylammonium iodide (see Example 18).



Example 18

2,6 - Dimethylphenol (122 g.) was added to a solution of sodium (23 g.) in ethanol (350 ml.). The mixture was heated to boiling and ethyl α - bromopropionate (181 g.) was gradually added. A vigorous reaction took place whilst a thick sludge separated and subsequently broke up. The final mixture was heated to reflux for 2 hours; it was then cooled and poured into water. The resulting α-2,6-dimethyl - phenoxypropionate was isolated with ether as an oil, boiling point 133—138°/14 mm.

This ester (100 g.) was slowly added to a suspension of lithium aluminium hydride (16 g.) in dry ether (600 ml.). After the addition was complete, the mixture was heated to reflux for 1 hour, then cooled and treated very cautiously with ethyl acetate to decompose the excess lithium aluminium hydride. Water was then added drop by drop until the decomposition was complete and then the mixture was acidified with concentrated hydrochloric acid. The ethereal layer was separated, dried over potassium carbonate, filtered and evaporated to give 2 - 2¹,6¹ - dimethylphenoxypropan - 1 - ol, boiling point 135—140°/15 mm.

A solution of this alcohol (20 g.) and pyridine (6.8 g.) in chloroform (15 ml.) was cooled to 0° and thionyl chloride (13.2 g.) slowly added over a period of 1 hour. The mixture was stood at room temperature for 2 hours and then heated on a steam-bath for 2 hours. After cooling, it was poured into water and the product isolated with ether. The 1-chloro - 2 - 2¹,6¹ - dimethylphenoxypropane had a boiling point of 130—134°/18 mm.

This substance (14.6 g.) was added to a suspension of aluminium chloride (10 g.) in carbon disulphide (40 ml.) with stirring Benzoyl chloride (10.3 g.) was then added over a period of 30 minutes and the mixture heated to reflux for 30 minutes. The reaction mixture was decomposed in the usual way with ice and hydrochloric acid; the carbon disulphide was removed in steam. The residue was dissolved in ether and the resulting solution washed exhaustively with 2*N*-sodium hydroxide. The residual ethereal solution was washed with water, dried over potassium carbonate, filtered and evaporated to give 2 - (4-benzoyl-2,6 - dimethylphenoxy) - 1 - chloropropane.

A solution of this compound (5.1 g.) in methanolic dimethylamine (33% w/w; 50 ml.) was heated to 145° for 6 hours in an autoclave. The resultant mixture was evaporated and the residue was treated with excess 2*N*-hydrochloric acid. The insoluble material was removed with ether and the aqueous layer was

basified to give 2 - (4 - benzoyl - 2,6 - di - methylphenoxy) - 1 - dimethylaminopropane which was isolated with ether, boiling point 162—176°/0.1 mm.

Methyl iodide (2 g.) was added to a solution of this base (2.8 g.) in acetone (5 ml.). After 30 minutes the solution was heated to reflux for 1 hour. On cooling a mass of crystals separated. These were filtered off, washed with ethyl acetate and crystallised twice from ethanol, once from water and then twice from ethanol. The resulting *N* - (2 - 4¹ - benzoyl - 2¹,6¹ - dimethylphenoxy - 2 - methylethyl) *N,N,N* - trimethylammonium iodide had a melting point 167°.

This melting point was undepressed on admixture with the iodide of the same melting point described in the preceding Example; the identity of this latter substance is thereby determined. The structure of the isomeric material of melting point 215—216° must therefore be *N* - (2 - 4¹ - benzoyl - 2¹,6¹ - dimethylphenoxy - 1 - methylethyl) - *N,N,N* - trimethylammonium iodide.

EXAMPLE 19

Stannous chloride (1.7 g.) was added to a suspension of *N* - (2 - 2¹,6¹ - dimethyl - 4¹ - *p* - nitrobenzoylphenoxyethyl) - *N,N,N* - trimethylammonium bromide (1.0 g.) in water (10 ml.) containing concentrated hydrochloric acid (3 ml.). The mixture was heated to boiling for 30 minutes. The original white suspension changed to rather a yellowish one. After cooling, hydrogen sulphide was passed through the mixture to remove the stannous and stannic salts which were filtered off. The filtrate was evaporated *in vacuo*. The residue was dissolved in water and the solution filtered to remove a little scum. It was carefully neutralised with ammonia and potassium iodide (1 g.) added to give a precipitate of *N* - (2 - 4¹ - *p* - aminobenzoyl - 2¹,6¹ - dimethylphenoxyethyl) - *N,N,N* - trimethylammonium iodide. It was recrystallised from methanol and ether; the melting point varied with the rate of heating but using a path preheated to 220° and a steady rise of about 2° per minute, the melting point was fairly constant at 239—241°.

EXAMPLE 20

1 - Bromo - 2 - *o* - bromophenoxyethane (28 g.) was added gradually to a stirred suspension of aluminium chloride (13.5 g.) in carbon disulphide (120 ml.); it was followed, still gradually, by benzoyl chloride (14.1 g.) over a period of 40 minutes. After standing at room temperature for a further hour, the mixture was heated to reflux for 2 hours. It was then cooled, poured on to ice and the carbon disulphide removed in steam. The residue was taken up into ether, the acidic products were removed with 2*N* - sodium hydroxide and the residual ethereal solution dried over magnesium sulphate, filtered and evaporated. The resulting 1 - (4 - benzoyl - 2 - bromophenoxy) - 2 - bromoethane was crystallised twice from methanol and twice from benzene and light petroleum (boiling point 60—80°); the final product had a melting point of 93—95°.

This product was reacted with methanolic dimethylamine as in Example 1 to give 1 - (4-benzoyl - 2 - bromophenoxy) - 2 - dimethylaminoethane, which was purified as its hydrogen oxalate, melting point 172—173°, since the base appeared to decompose on attempted distillation. Treatment of this hydrogen oxide with excess ammonia and isolation of the precipitated oil with ether gave pure 1 - (4 - benzoyl - 2 - bromphenoxy) - 2-dimethylaminoethane.

This base (3 g.) was reacted with methyl iodide (1.8 g.) in acetone (9 ml.). The mixture rapidly set solid. More acetone (5 ml.) was added and the mixture was heated to reflux for 10 minutes. The resulting *N* - (2 - 4¹ - benzoyl - 2¹ - bromphenoxyethyl) - *N,N,N* - trimethylammonium iodide was recrystallised from methanol, melting point 209—210°.

EXAMPLE 21

1 - (4 - Benzoyl - 2 - bromophenoxy) - 2 - dimethylaminoethane (2 g.) was reacted with ethyl iodide (1.3 g.) in boiling acetone (5 ml.) for 30 minutes. The resulting semi-solid mass was filtered to give *N* - (2 - 4¹ - benzoyl - 2¹ - bromophenoxyethyl) - *N* - ethyl - *N,N* - dimethylammonium iodide, melting point 165—166°.

EXAMPLE 22

By stages similar to those described in Example 20, 1 - bromo - 2 - *o* - chlorophenoxyethane was converted into 1 - (4 - benzoyl - 2 - chlorophenoxy) - 2 - bromoethane, boiling point 198—204°/0.1 mm., which subsequently solidified and was recrystallised from a mixture of benzene and light petroleum (boiling point 40—60°), melting point 77.5—78.5°. This was then converted into *N* - (2 - 4¹ - benzoyl - 2¹ - chlorophenoxyethyl) - *N,N,N*-trimethylammonium bromide, melting point 199—200° (from isopropanol and ether) by the methods described in Examples 3 and 4.

EXAMPLE 23

By methods similar to those described in Example 20, 1 - bromo - 2 - *o* - fluorophenoxyethane was converted into 1 - (4 - benzoyl - 2 - fluorophenoxy) - 2 - bromoethane, melting point 98—100°; and thence into 1-(4 - benzoyl - 2 - fluorophenoxy) - 2 - dimethylaminoethane, which was purified as its hydrogen oxalate which was recrystallised from methanol, melting point 154—155°. The regenerated base reacted with methyl iodide to give N - (2,4¹ - benzoyl - 2¹ - fluorophenoxyethyl) - *N,N,N* - trimethylammonium iodide, melting point 227—228°.

EXAMPLE 24

By methods similar to those described in Example 21, 1 - (4 - benzoyl - 2 - fluoro - phenoxy) - 2 - dimethylaminoethane (1.8 g.) was reacted with ethyl iodide (1.3 g.) to give

N - (2 - 4¹ - benzoyl - 2¹ - fluorophenoxy - ethyl) - *N* - ethyl - *N,N* - dimethylammonium iodide semihydrate, melting point 203—204°, with softening at 135°. On drying at 60° *in vacuo* the melting point was 211—212°.

EXAMPLE 25

4 - Hydroxy - 3 - methylbenzophenone (11 g.) was dissolved in a mixture of glacial acetic acid (60 ml.) and chloroform (400 ml.). The resulting solution was cooled to 15° and bromine (3 ml.) was slowly added with stirring. After 2 hours the final mixture was warmed to 50° for 1 hour. The resulting solution was washed with water, sodium bisulphite solution and finally with sodium bicarbonate solution. It was then dried over sodium sulphate, filtered and evaporated. The residual 3-bromo-4 - hydroxy - 5 - methylbenzophenone was crystallised from methanol, melting point 124—125°.

This substance (13 g.) was added to toluene (50 ml.) together with 1 - chloro - 2 - dimethylaminoethane hydrochloride (8.2 g.) and flake sodium hydroxide (4.8 g.) and the resulting mixture was heated to reflux with stirring for 24 hours. Water was added to the cooled mixture to remove the inorganic layer. The toluene layer was separated and exhaustively extracted with 2*N* - hydrochloric acid. The combined acid extracts were basified and the precipitated 1 - (4 - benzoyl - 2 - bromo - 6 - methylphenoxy) - 2 - dimethylaminoethane was isolated with ether, boiling point 180—182°/0.15 mm.

Methyl iodide (0.7 g.) was added to a solution of this base (1.2 g.) in acetone (3 ml.). A crystalline solid rapidly separated. After standing overnight at room temperature, ether (1 ml.) was added. The resulting *N* - (2 - 4¹ - bezoyl - 2¹ - bromo - 6¹ - methylphenoxy - ethyl) - *N,N,N* - trimethylammonium iodide was filtered off and recrystallised from a mixture of ethanol and isopropanol (1 : 1), melting point 178—179°.

EXAMPLE 26

2 - Ethyl - 6 - methylphenol was reacted with benzoyl chloride in pyridine to yield 2 - ethyl - 6 - methylphenylbenzoate, boiling point 126°/0.15 mm.

Powdered aluminium chloride (11 g.) was added to this benzoate (10 g.) with stirring and the resulting mixture slowly heated to *ca.* 90° when a reaction apparently occurred. After 1 hour at this temperature, the mixture was heated to 150° for 1 hour and then cooled and decomposed with water and hydrochloric acid. The resulting 3 - ethyl - 4 - hydroxy - 5 - methyl - benzophenone was purified by crystallisation from benzene and light petroleum (boiling point, 40—60°), followed by sublimation *in vacuo* and recrystallisation from benzene and then from light petroleum (boiling point 40—60°) to give a colourless product, melting point 129—130°. This was reacted with 1 - chloro - 2 - dimethylaminoethane hydrochloride (0.8 g.) as in Example 25 to give 1 - (4 - benzoyl - 2 - ethyl - 6 - methylphenoxy) - 2 - dimethylaminoethane, boiling point 166—172°/0.1 mm. Its hydrochloride crystallised from ethanol, melting point 148—149.5°.

This base (1 g.) was dissolved in acetone (2 ml.) and dimethyl sulphate (0.5 g.) added to the residual solution to give *N* - (2 - 4¹ - benzoyl - 2¹ - ethyl - 6¹ - methylphenoxy - ethyl) - *N,N,N* - trimethylammonium methosulphate, melting point 94—96° with previous softening. On drying at 60° *in vacuo* the melting point rose to 117—119°. With aqueous potassium iodide the corresponding iodide resulted, melting point 156—157°.

With ethyl iodide (1.3 g.), the tertiary base (2 g.) gave *N* - (2-4¹ - benzoyl - 2¹-ethyl - 6¹-methylphenoxyethyl) - *N* - ethyl - *N,N* - dimethylammonium iodide, melting point 221—222°.

EXAMPLE 27

A suspension of 1 - (4 - benzoyl - 2,6 - dimethylphenoxy) - 2 - bromoethane (20 g.) in methanolic methylamine (33% w/w; 30 g.) was heated at 100° for 3 hours in a sealed autoclave. The resulting mixture was evaporated on a steam-bath. The residue was basified with excess aqueous sodium hydroxide and the precipitated oil was extracted with ether. The ethereal solution was exhaustively extracted with 4*N* - hydrochloric acid. The combined acid extracts were basified with aqueous sodium hydroxide and the resulting oil isolated with ether to give 1 - (4 - benzoyl - 2,6 - dimethylphenoxy) - 2 - methylaminoethane, boiling point 180—190°/0.15 mm. Its hydrogen oxalate crystallised from methanol and ether, melting point 198°. The parent base (10 g.) was added to a slurry of anhydrous sodium carbonate (11.2 g.) in methanol (30 ml.). Methyl iodide (20 g.) was added and the resulting mixture was heated to reflux for 2 hours and then filtered whilst still hot. The filtrate rapidly crystallised. The resulting *N*-(2-4¹ - benzoyl 2¹,6¹ - dimethylphenoxyethyl)-*N,N,N* - trimethylammonium iodide was recrystallised from ethanol and was identical with the product described in Example 1.

EXAMPLE 28

A suspension of 2,4 - dihydroxybenzophenone (16.3 g.), 1 - chloro - 2 - dimethylaminoethane hydrochloride (14.4 g.) and flake sodium hydroxide (8 g.) in toluene (100 ml.) was heated to reflux for 24 hours with vigorous stirring. Water was added to the cooled mixture, the mixture vigorously stirred and the aqueous layer removed. The residual organic layer was diluted with ether and exhaustively extracted with 2*N* - hydrochloric acid. The combined acid extracts were basified with aqueous sodium carbonate and the precipitated gum was isolated with ether. The resulting base was reacted directly with methyl iodide

(15.0 g.) in acetone (30 ml.) to give *N* - (2-4¹ - benzoyl - 3¹ - hydroxyphenoxyethyl) - *N*, *N*,*N* - trimethylammonium iodide, melting point 139—140° (from ethanol).

EXAMPLE 29

A mixture of 1 - (4 - benzoyl - 2,6 - dimethylphenoxy) - 2 - bromoethane (33.3 g.), methylaminoethanol (18.8 g.) and benzene (30 ml.) was heated on a steam-bath for 2 hours. After cooling, the resulting mixture was shaken with excess 10*N* - sodium hydroxide and the aqueous layer removed. The residual organic layer was evaporated. The residual crude base, 1 - (4 - benzoyl - 2,6 - dimethylphenoxy) - 2-(*N* - 2 - hydroxyethyl - *N* - methylamino) - ethane could not be distilled *in vacuo*, neither could it be purified as an acid addition salt. It was therefore reacted directly with methyl iodide (18.0 g.) in acetone (30 ml.) to give *N* - (2 - 4¹ - benzoyl - 2¹,6¹ - dimethylphenoxyethyl) - *N* - 2 - hydroxyethyl - *N*,*N* - dimethylammonium iodide, melting point 160—161°, (from ethanol).

EXAMPLE 30

By processes analogous to those described in Example 29, 1 - (4 - benzoyl - 2,6 - dimethylphenoxy) - 2 - bromoethane (30 g.) was reacted with diethan - 2 - olamine (19.5 g.) to give 1 - (4 - benzoyl - 2,6 - dimethyl - phenoxy) - 2 - (*N*,*N* - bis - 2 - hydroxyethylamino) - ethane. This base could not be purified as an acid addition salt and was reacted directly with methyl iodide (19.0 g.) to give *N* - (2 - 4¹ - benzoyl - 2¹,6¹ - dimethyl - phenoxyethyl) - *N*,*N* - bis - (2 - hydroxy - ethyl) - *N* - methylammonium iodide, melting point 110—111°.

EXAMPLE 31

1 - (4 - Benzoyl - 2,6 - dimethylphenoxy)-2 - bromoethane (20 g.) was added to a solution of diethylamine (22 g.) in ethanol (100 ml.) and the resulting mixture heated in a sealed autoclave for 6 hours at 100°. The mixture was subsequently evaporated and excess 4*N* - sodium hydroxide solution added to the residue. The desired 1 - (4 - benzoyl - 2, 6 - dimethylphenoxy) - 2 - diethylaminoethane was isolated with ether as an oil, boiling point 168—172°/0.02 mm.

Methyl iodide (7 g.) was added to a solution of this base (6.5 g.) in acetone (30 ml.) when a spontaneous reaction occurred. After 15 minutes, the mixture was heated to reflux for 15 minutes and then diluted with ether. The resulting *N* - (2-4¹ - benzoyl - 2¹,6¹-dimethylphenoxyethyl) - *N*,*N* - diethyl - *N* - methylammonium iodide was filtered off and recrystallised twice from ethanol, melting point 149—150°.

EXAMPLE 32

4 - Hydroxy - 3 - methoxybenzophenone (32 g.) was added to a solution of sodium (2.3 g.) in ethanol (100 ml.). A semi-solid mass resulted and water (20 ml.) was added to produce a clear solution to which ethylene dibromide (23 g.) was added. The resulting mixture was heated to reflux for 8 hours. After cooling the insoluble material was filtered off, and washed with a little fresh methanol. The combined filtrate and washings were poured into water and the precipitated oil was extracted with ether. The ethereal solution was washed exhaustively with *N* - sodium hydroxide solution to remove unchanged starting material; the residual ethereal solution was washed with water, dried over potassium carbonate, filtered and evaporated.

The residue was distilled *in vacuo*, boiling point 190—205°/0.001 mm. The resulting 1-(4 - benzoyl - 2 - methoxyphenoxy) - 2 - bromoethane subsequently solidified and was repeatedly recrystallised from methanol, melting point 103—104°.

A suspension of this product (5 g.) in alcoholic trimethylamine (50% w/w; 20 ml.) was heated in a sealed tube to 100° for 10 hours. After cooling, the resulting mixture was diluted with ether and the resulting solid was filtered off, washed with ethyl acetate and dried *in vacuo*. It was recrystallised from isopropanol (some insoluble material being filtered off), melting point 172—174° with clearing at 176°. This product, *N* - (2 - 4¹ - benzoyl - 2¹ - methoxyphenoxyethyl) - *N*,*N*,*N* - trimethylammonium bromide was dissolved in warm water (5 ml.) and added to a solution of potassium iodide (1 g.) in water (5 ml.). An oil separated and rapidly crystallised. The resulting *N* - (2 - 4¹ - benzoyl - 2¹ - methoxyphenoxyethyl) - *N*,*N*,*N* - trimethylammonium iodide was crystallised from a mixture of ethanol and ether and then from hot water, melting point, 189—190°.

EXAMPLE 33

Finely divided silver chloride (freshly prepared from silver nitrate) (2.1 g.) was added to a suspension of *N* - (2 - 4¹ - benzoyl - 2¹, 6¹ - dimethylphenoxyethyl) - *N*,*N*,*N* - tri - methylammonium iodide (1.1 g.) in methanol-water mixture (1 : 1; 10 ml.). The resulting suspension was heated to reflux for 30 minutes, filtered and the residue washed with fresh methanol. The combined filtrate and washings were evaporated *in vacuo* and the residual solid was recrystallised from isopropanol and ether to give *N* - (2 - 4¹ - benzoyl - 2¹,6¹ - dimethylphenoxyethyl) - *N*,*N*,*N* - trimethyl - ammonium chloride monohydrate, melting point 209°.

EXAMPLE 34

Dimethyl sulphate (7 g.) was added to a solution of 1 - (4 - benzoyl - 2,6 - dimethylphenoxy) - 2 - dimethylaminoethane (10 g.) in dry acetone (20 ml.). After standing for 15 minutes the mixture was heated to reflux for

40 minutes. On cooling a semi-solid mass of methosulphate was formed. This was filtered and the residue was washed with ethyl acetate and then recrystallised by precipitation from warm ethanol with ethyl acetate, melting point 138—139°.

EXAMPLE 35

4 - Hydroxy - 3,5 - dimethylacetophenone (32.8 g.) was added to a solution of sodium (4.6 g.) in ethanol (100 ml.). Ethylene dibromide (45 g.) was then added and the resulting mixture was heated to reflux for 5½ hours. After cooling, it was then poured into water to precipitate an oil which was extracted with ether. After washing with 2*N*-sodium hydroxide, to remove unchanged starting material, the ethereal solution was dried, filtered, and evaporated. The residue was distilled in to give 1 - (4 - acetyl - 2,6 - dimethylphenoxy) - 2 - bromoethane, boiling point 135—145°/0.05 mm.; it subsequently solidified, freezing point 52°. This ether (9.0 g.) was added gradually to a stirred solution of dimethylamine in methanol (50% w/w; 15 g.). The final mixture was maintained at room temperature for 7 days and then evaporated on a steam-bath. Excess 4*N* - ammonia was added to the residue to precipitate an oil which was taken up into ether. The ethereal extract was dried over potassium carbonate, filtered and evaporated. The residue was distilled *in vacuo* to give 1 - (4 - acetyl - 2,6 - dimethylphenoxy) - 2 - dimethylaminoethane, boiling point 118—120°/0.1 mm.

Methyl iodide (5.0 g.) was added to a solution of this base (5.0 g.) in acetone (5 ml.). A vigorous reaction took place and an oil separated and subsequently solidified. The resulting *N* - (2 - 4¹ - acetyl - 2¹,6¹ - dimethylphenoxyethyl) - *N,N,N* - trimethylammonium iodide was recrystallised from ethanol. It was first obtained in a form of melting point 169—170°, but subsequently a second and apparently more stable crystalline state, melting point 182—183°, resulted.

EXAMPLE 36

By processes analogous to those described in Example 35, 4 - hydroxy - 3,5 - dimethylpropiophenone was converted into 1 - bromo-2 - (2,6 - dimethyl - 4 - propionylphenoxy) ethane, boiling point 150—165°/0.1 mm. which solidified and was recrystallised from isopropanol, melting point 49—50°. Reaction with excess methanolic dimethylamine then gave 1 - dimethylamino - 2 - (2,6 - dimethyl-4 - propionylphenoxy)ethane, boiling point 124—127°/0.1 mm.

Methyl iodide (6.0 g.) was added to a solution of this base (5.0 g.) in acetone (10 ml.). A vigorous reaction ensued with the separation of *N* - (2 - 2¹,6¹ - dimethyl - 4¹ - propionylphenoxyethyl) - *N,N,N* - trimethylammonium iodide. It was recrystallised from ethanol, melting point 181—182°.

EXAMPLE 37

A solution of 1 - bromo - 2 - (2,6 - di - methyl - 4 - propionylphenoxy) - ethane (5.7 g.) and ethyldimethylamine (2.5 g.) in methyl ethylketone (10 ml.) was heated to reflux for 2 hours. The addition of ether to the reaction medium precipitated an oil which subsequently crystallised. This deliquescent solid was filtered off and recrystallised from a mixture of isopropanol and ether to give *N* - (2 - 2¹,6¹-dimethyl - 4¹ - propionylphenoxyethyl) - *N*-ethyl - *N,N* - dimethylammonium bromide, melting point 109—111°.

EXAMPLE 38

By reacting phenacetyl chloride with an equimolecular amount of 2,6 - dimethylphenol in pyridine there was obtained 2,6 - dimethylphenyl phenacetate, boiling point 162—178°/15 mm., freezing point 38°. A mixture of this ester (24 g.) and powdered aluminium chloride (21 g.) was heated in an oil bath (with stirring) for 2 hours at 120° and the resulting viscous mass was then decomposed with dilute hydrochloric acid in the usual way to give 4-hydroxy - 3,5 - dimethyldeoxybenzoin which was crystallised from a mixture of methanol and water (3 : 1), melting point 114—116°. By processes analogous to those described in Example 35, this hydroxyketone was converted into 1 - bromo - 2 - (2,6 - dimethyl - 4 - phenacetylphenoxy)ethane, boiling point 200—210°/0.1 mm. It subsequently solidified and was recrystallised from methanol, melting point 87—88°.

1 - Bromo - 2 -(2,6 - dimethyl - 4 - phenacetylphenoxy)ethane (3.5 g.) was added to ethanolic trimethylamine (33% w/w; 5.4 g.) and the resulting mixture heated to 100—110° for 12 hours in a sealed tube. The crude reaction mixture was evaporated *in vacuo* and the residue ground with ethyl acetate, when it crystallised. This solid product, *N* - (2 - 2¹,6¹-dimethyl - 4¹ - phenacetylphenoxyethyl) - *N,N,N* - trimethylammonium bromide, was recrystallised from isopropanol, melting point 148—150° (softening 125°).

EXAMPLE 39

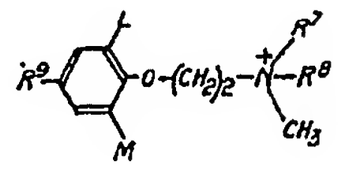
A mixture of ethyl 4 - hydroxybenzoate (4.95 g.), 1 - chloro - 2 - dimethylamino - ethane hydrochloride (5.76 g.) and sodium hydroxide flake (3.2 g.) was heated in boiling toluene (25 ml.) with stirring for twenty hours. After cooling, dilute hydrochloric acid was added, and the separated acid layer was treated with ice and concentrated ammonia solution. The liberated 4 - ethoxycarbonylphenoxy - 2 - dimethylaminoethane was isolated by means of chloroform and was distilled, boiling point 131°/0.05 mm.

This base (2 g.) was dissolved in acetone (20 ml.) and treated with methyl iodide (1.5 ml.). An immediate reaction occurred, with precipitation of a colourless salt. Crystallisa-

tion from a mixture of ethanol and ethyl acetate give *N* - (2 - 4[1] - ethoxycarbonylphenoxyethyl) - *N,N,N* - trimethylammonium iodide as needles, melting point 157—160°.

In Table II are listed additional *N* - 4 - substituted - phenoxyethyl - *N,N,N* - trialkylammonium iodides which were prepared by the method described in Example 39, that is by the methylation of the corresponding intermediate tertiary amines, whose boiling points where not previously described in the literature are indicated, except for Examples 50 and 52 which were prepared by the ethylation of the intermediate tertiary amines used respectively in Examples 49 and 51.

TABLE II



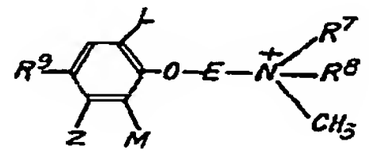
Example No.	R_9	L	M	R_7	R_8	Boiling point of the intermediate tertiary amine	Solvent of crystallisation	Melting point of the quaternary ammonium iodide
40	$CH_3O.CO$	H	H	CH_3	CH_3	124°/0.1 mm.	acetone/ethyl acetate	205—207°
41	$CH_3O.CO$	CH_3	H	CH_3	CH_3	114°/0.05 mm.	ethanol/ethyl acetate	149—151°
42	$CH_3O.CO$	CH_3	CH_3	CH_3	CH_3	129°/0.2 mm.	ethanol/ethyl acetate	213—215°
43	$C_2H_5O.CO$	H	H	C_2H_5	C_2H_5	—	ethanol/ethyl acetate	128°
44	$C_2H_5O.CO$	CH_3	H	CH_3	CH_3	121°/0.01 mm.	ethanol/ethyl acetate	163—165°
45	*iso*$C_3H_7O.CO$	CH_3	CH_3	CH_3	CH_3	120°/0.01 mm.	isopropanol	186—187°
46	$CH_3O.CO$	CH_3O	H	CH_3	CH_3	124°/0.1 mm.	ethanol	181—184°
47	$C_2H_5O.CO$	CH_3O	H	CH_3	CH_3	124°/0.01 mm.	ethanol	136—138°
48	$C_2H_5O.CO$	CH_3O	CH_3O	CH_3	CH_3	134°/0.01 mm.	ethanol	208—210°
49	$CH_3O.CO$	Br	H	CH_3	CH_3	142°/0.2 mm.	ethanol	196—199°
50	$CH_3O.CO$	Br	H	CH_3	C_2H_5	—	ethanol	186—189°
51	$C_2H_5O.CO$	Br	H	CH_3	CH_3	139°/0.1 mm.	isopropanol	184—185°
52	$C_2H_5O.CO$	Br	H	CH_3	C_2H_5	—	isopropanol	121—124°
53	$CH_3CO.NH$	CH_3	CH_3	CH_3	CH_3	160°/0.08 mm.	methanol	242—244°
54	$C_2H_5CO.NH$	CH_3	CH_3	CH_3	CH_3	168°/0.08 mm.	ethanol	197—199°

EXAMPLE 55

A mixture of 1 - bromo - 2 - (4 - ethoxycarbonyl - 2,6 - dimethylphenoxy)ethane (9 g.) and trimethylamine (33% w/w; 30 ml.) solution in ethanol was heated in a sealed tube at 100° for 8 hours. Addition of ether to the contents precipitated a bromide, which was dissolved in water and converted to the sparingly soluble iodide by treatment with excess of potassium iodide solution. The precipitated *N* - (2 - 4¹ - ethoxycarbonyl - 2¹,6¹ - dimethylphenoxyethyl) - *N*,*N*,*N* - trimethylammonium iodide separated from ethanol/ethyl acetate mixtures in colourless plates, melting point 177—179°.

WHAT WE CLAIM IS:—

1. A method for the preparation of a quaternary ammonium compound, containing a cation of the formula:



wherein R^7 and R^8 are the same or different and are each methyl, ethyl, or 2 - hydroxyethyl groups; and

R^9 is an acetyl, phenacetyl, propionyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, acetamido, or propionamido group in the circumstances when E is a $—CH_2—CH_2—$ group, and L and M are the same or different and are each hydrogen or halogen atoms or methyl, ethyl, or methoxy groups, and Z is a hydrogen atom; or

R^9 is a benzoyl group (wherein the phenyl group is optionally substituted in any one position by a halogen atom or alkyl or alkoxy group, containing from one to four carbon atoms, or a nitro group) in the circumstances when E is a

$—CH_2—CH_2—$, $—CH_2—CH_2—CH_2—$,

$—CH(CH_3)—CH_2—$ or $—CH_2—CH(CH_3)—$

group, and L and M are the same or different and are each hydrogen or halogen atoms or methyl, ethyl, or methoxy groups, and Z is a hydrogen atom or a hydroxy group, characterised in that it comprises a quaternisation reaction, that is a reaction of a tertiary amine (which may be formed *in situ*) containing three of the four groups desired in the quaternary ammonium compound with a reactive ester of the hydroxy derivative of the group it is desired to introduce.

2. A method as claimed in claim 1 comprising the reaction of a tertiary amine with a reactive ester of the hydroxy derivative of the phenoxyalkyl, R^7, R^8, or methyl group.

3. A method as claimed in claim 1 comprising the reaction of a phenoxyalkyl secondary amine with a reactive ester of methanol or ethanol or a reactive mono-ester of ethylene glycol, which consists of the formation of a tertiary amine *in situ* and its subsequent quaternisation.

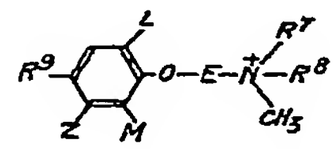
4. A method as claimed in claim 1 comprising the reaction of a primary phenoxyalkylamine with a reactive ester of methanol, which consists of the formation of a tertiary amine *in situ* and its subsequent quaternisation.

5. A modification of the method of preparation claimed in claim 1 for preparation of the compounds of the formula defined in claim 1 wherein R^9 is also to be a benzoyl group carrying a free amino group, characterised in that in the reactants taking part in the quaternisation reaction there is present in R^9 instead of the free amino group itself a nitro group which is subsequently reduced to the desired free amino group.

6. A pharmaceutical preparation comprising a quaternary ammonium compound containing a cation of the formula defined in claims 1 and 5 together with a suitable carrier therefor.

7. A method for the preparation of a pharmaceutical preparation as claimed in claim 6 comprising the inclusion of a quaternary ammonium compound containing a cation of the fmula defined in claims 1 and 5 in a suitable carrier therefor.

8. A quaternary ammonium compound containing a cation of the formula:



wherein R^7 and R^8 are the same or different and are each methyl, ethyl, or 2 - hydroxyethyl groups; and

R^9 is an acetyl, phenacetyl, propionyl, methoxycarbonyl, isopropoxycarbonyl, ethoxycarbonyl, acetamido, or propionamido group in the circumstances when E is a $—CH_2—CH_2—$ group, and L and M are the same or different and are each hydrogen or halogen atoms or methyl, ethyl, or methoxy groups, and Z is a hydrogen atom;

R^9 is a benzoyl group (wherein the phenyl group is optionally substituted in any one position by a halogen atom or alkyl or alkoxy group, containng from one to four carbon atoms, or a nitro or free amino group) in the circumstances when E is a

$—CH_2—CH_2—$, $—CH_2—CH_2—CH_2—$,

$—CH(CH_3)—CH_2—$ or $—CH_2—CH(CH_3)—$

group, and L and M are the same or different and are each hydrogen or halogen atoms

or methyl, ethyl, or methoxy groups, and Z is a hydrogen atom or a hydroxy group.

9. A quaternary ammonium compound containing the *N* - (2 - 4¹ - benzoyl - 2¹,6¹ - dimethylphenoxyethyl) - *N*,*N*,*N* - trimethyl - ammonium cation.

10. A quaternary ammonium compound containing the *N* - (2 - 4¹ - benzoyl - 2¹ - bromophenoxyethyl) - *N*,*N*,*N* - trimethyl - ammonium cation.

11. A quaternary ammonium compound containing the *N* - (2 - 4¹ - benzoyl - 2¹ - bromophenoxyethyl) - *N* - ethyl - *N*,*N* - dimethylammonium cation.

12. A quaternary ammonium compound containing the *N* - (2 - 4¹ - benzoyl - 2¹ - bromo - 6¹ - methylphenoxyethyl) - *N*,*N*,*N* - trimethylammonium cation.

13. A quaternary ammonium compound containing the *N* - (2 - 4¹ - *p* - methoxy - benzoyl - 2¹,6¹ - dimethylphenoxyethyl) - *N*,*N*,*N* - trimethylammonium cation.

14. A quaternary ammonium compound containing the *N* - (2 - 4¹ - ethoxycarbonyl-2¹,6¹ - dimethylphenoxyethyl) - *N*,*N*,*N* - trimethylammonium cation.

15. A quaternary ammonium compound containing the *N* - (2 - 4¹ - acetamido - 2¹,6¹-dimethylphenoxyethyl) - *N*,*N*,*N* - trimethyl - ammonium cation.

16. A method for the preparation of a quaternary ammonium compound containing a cation of the formula defined in claims 1 and 5 substantially as hereinbefore described with reference to any one of the foregoing examples.

17. A quaternary ammonium compound containing a cation of the formula defined in claims 1 and 5 when prepared by a method of preparation substantially as herein described and ascertained or any obvious chemical equivalent.

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